

who were receiving a sulfonylurea drug at the time of delivery. This has been reported more frequently with the use of agents with prolonged half-lives. If MICRONASE is used during pregnancy, it should be discontinued at least two weeks before the expected delivery date.

Nursing Mothers

Although it is not known whether glyburide is excreted in human milk, some sulfonylurea drugs are known to be excreted in human milk. Because the potential for hypoglycemia in nursing infants may exist, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. If the drug is discontinued, and if diet alone is inadequate for controlling blood glucose, insulin therapy should be considered.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Hypoglycemia: See Precautions and Overdosage Sections.

Gastrointestinal Reactions: Cholestatic jaundice and hepatitis may occur rarely; MICRONASE Tablets should be discontinued if this occurs.

Liver function abnormalities, including isolated transaminase elevations, have been reported.

Gastrointestinal disturbances, eg, nausea, epigastric fullness, and heartburn are the most common reactions, having occurred in 1.8% of treated patients during clinical trials. They tend to be dose related and may disappear when dosage is reduced.

Dermatologic Reactions: Allergic skin reactions, eg, pruritus, erythema, urticaria, and morbilliform or maculopapular eruptions occurred in 1.6% of treated patients during clinical trials. These may be transient and may disappear despite continued use of MICRONASE; if skin reactions persist, the drug should be discontinued.

Porphyria cutanea tarda and photosensitivity reactions have been reported with sulfonylureas.

Hematologic Reactions: Leukopenia, agranulocytosis, thrombocytopenia, hemolytic anemia, aplastic anemia, and pancytopenia have been reported with sulfonylureas.

Metabolic Reactions: Hepatic porphyria and disulfiram-like reactions have been reported with sulfonylureas; however, hepatic porphyria has not been reported with MICRONASE and disulfiram-like reactions have been reported very rarely.

Cases of hyponatremia have been reported with glyburide and all other sulfonylureas, most often in patients who are on other medications or have medical conditions known to cause hyponatremia or increase release of antidiuretic hormone. The syndrome of inappropriate antidiuretic hormone (SIADH) secretion has been reported with certain other sulfonylureas, and it has been suggested that these sulfonylureas may augment the peripheral (antidiuretic) action of ADH and/or increase release of ADH.

Other Reactions: Changes in accommodation and/or blurred vision have been reported with glyburide and other sulfonylureas. These are thought to be related to fluctuation in glucose levels.

In addition to dermatologic reactions, allergic reactions such as angioedema, arthralgia, myalgia and vasculitis have been reported.

OVERDOSAGE

Overdosage of sulfonylureas, including MICRONASE Tablets, can produce hypoglycemia. Mild hypoglycemic symptoms, without loss of consciousness or neurological findings, should be treated aggressively with oral glucose and adjustments in drug dosage and/or meal patterns. Close monitoring should continue until the physician is assured that the patient is out of danger. Severe hypoglycemic reactions with coma, seizure, or other neurological impairment occur infrequently, but constitute medical emergencies requiring immediate hospitalization. If hypoglycemic coma is diagnosed or suspected, the patient should be given a rapid intravenous injection of concentrated (50%) glucose solution. This should be followed by a continuous infusion of a more dilute (10%) glucose solution at a rate which will maintain the blood glucose at a level above 100 mg/dL. Patients should be closely monitored for a minimum of 24 to 48 hours, since hypoglycemia may recur after apparent clinical recovery.

DOSAGE AND ADMINISTRATION

There is no fixed dosage regimen for the management of diabetes mellitus with MICRONASE Tablets or any other hypoglycemic agent. In addition to the usual monitoring of urinary glucose, the patient's blood glucose must also be monitored periodically to determine the minimum effective dose for the patient; to detect primary failure, ie, inadequate lowering of blood glucose at the maximum recommended dose of medication; and to detect secondary failure, ie, loss of adequate blood glucose lowering response after an initial period of effectiveness. Glycosylated hemoglobin levels may also be of value in monitoring the patient's response to therapy.

Short-term administration of MICRONASE may be sufficient during periods of transient loss of control in patients usually controlled well on diet.

Usual Starting Dose

The usual starting dose of MICRONASE Tablets is 2.5 to 5 mg daily, administered with breakfast or the first main meal. Those patients who may be more sensitive to hypoglycemic drugs should be started at 1.25 mg daily. (See PRECAUTIONS section for patients at increased risk.) Failure to follow an appropriate dosage regimen may precipitate hypoglycemia. Patients who do not adhere to their prescribed dietary and drug regimen are more prone to exhibit unsatisfactory response to therapy.

Transfer From Other Hypoglycemic Therapy Patients Receiving Other Oral Antidiabetic Therapy: Transfer of patients from other oral antidiabetic regimens to MICRONASE should be done conservatively and the initial daily dose should be 2.5 to 5 mg. When transferring patients from oral hypoglycemic agents other than chlorpropamide to MICRONASE, no transition period and no initial or priming dose are necessary. When transferring patients from chlorpropamide, particular care should be exercised during the first two weeks because the prolonged retention of chlorpropamide in the body and subsequent overlapping drug effects may provoke hypoglycemia.

Patients Receiving Insulin: Some Type II diabetic patients being treated with insulin may respond satisfactorily to MICRONASE. If the insulin dose is less than 20 units daily, substitution of MICRONASE Tablets 2.5 to 5 mg as a single daily dose may be tried. If the insulin dose is between 20 and 40 units daily, the patient may be placed directly on MICRONASE Tablets 5 mg daily as a single dose. If the insulin dose is more than 40 units daily, a transition period is required for conversion to MICRONASE. In these patients, insulin dosage is decreased by 50% and MICRONASE Tablets 5 mg daily is started. Please refer to Titration to Maintenance Dose for further explanation.

Titration to Maintenance Dose

The usual maintenance dose is in the range of 1.25 to 20 mg daily, which may be given as a single dose or in divided doses (See Dosage Interval section). Dosage increases should be made in increments of no more than 2.5 mg at weekly intervals based upon the patient's blood glucose response.

No exact dosage relationship exists between MICRONASE and the other oral hypoglycemic agents. Although patients may be transferred from the maximum dose of other sulfonylureas, the maximum starting dose of 5 mg of MICRONASE Tablets should be observed. A maintenance dose of 5 mg of MICRONASE Tablets provides approximately the same degree of blood glucose control as 250 to 375 mg chlorpropamide, 250 to 375 mg tolazamide, 500 to 750 mg acetohexamide, or 1000 to 1500 mg tolbutamide.

When transferring patients receiving more than 40 units of insulin daily, they may be started on a daily dose of MICRONASE Tablets 5 mg concomitantly with a 50% reduction in insulin dose. Progressive withdrawal of insulin and increase of MICRONASE in increments of 1.25 to 2.5 mg every 2 to 10 days is then carried out. During this conversion period when both insulin and MICRONASE are being used, hypoglycemia may rarely occur. During insulin withdrawal, patients should test their urine for glucose and acetone at least three times daily and report results to their physician. The appearance of persistent acetonuria with glycosuria indicates that the patient is a Type I diabetic who requires insulin therapy.

Concomitant Glyburide and Metformin Therapy

MICRONASE Tablets should be added gradually to the dosing regimen of patients who have not responded to the maximum dose of metformin monotherapy after four weeks (see Usual Starting Dose and Titration to Maintenance Dose). Refer to metformin package insert.

With concomitant glyburide and metformin therapy, the desired control of blood glucose may be obtained by adjusting the dose of each drug. However, attempts should be made to identify the optimal dose of each drug needed to achieve this goal. With concomitant glyburide and metformin therapy, the risk of hypoglycemia associated with sulfonylurea therapy continues and may be increased. Appropriate precautions should be taken (see PRECAUTIONS section).

Maximum Dose

Daily doses of more than 20 mg are not recommended.

Dosage Interval

Once-a-day therapy is usually satisfactory. Some patients, particularly those receiving more than 10 mg daily, may have a more satisfactory response with twice-a-day dosage.

Specific Patient Populations

MICRONASE is not recommended for use in pregnancy or for use in pediatric patients.

In elderly patients, debilitated or malnourished patients, and patients with impaired renal or hepatic function, the initial and maintenance dosing should be conservative to avoid hypoglycemic reactions. (See PRECAUTIONS section.)

HOW SUPPLIED

MICRONASE Tablets are supplied as follows:

MICRONASE Tablets 1.25 mg (White, Round, Scored, imprinted MICRONASE 1.25)	NDC 0009-0181-01
Bottles of 100	
MICRONASE Tablets 2.5 mg (Dark Pink, Round, Scored, imprinted MICRONASE 2.5)	NDC 0009-0141-01
Bottles of 100	
Bottles of 500	NDC 0009-0141-11
Bottles of 1000	NDC 0009-0141-03
Unit Dose Pkg of 100	NDC 0009-0141-02
MICRONASE Tablets 5 mg (Blue, Round, Scored imprinted MICRONASE 5)	NDC 0009-0171-11
Bottles of 30	NDC 0009-0171-12
Bottles of 60	NDC 0009-0171-05
Bottles of 100	NDC 0009-0171-06
Bottles of 500	NDC 0009-0171-07
Bottles of 1000	NDC 0009-0171-03
Unit Dose Pkg of 100	NDC 0009-0171-03
Caution: Federal law prohibits dispensing without prescription. Store at controlled room temperature 20° to 25° C (68° to 77° F) [see USP]. Dispensed in well closed containers with safety closures. Keep container tightly closed.	
Pharmacia & Upjohn Company	
Kalamazoo, MI 49001, USA	
Revised May 1997	811 985 420 691015

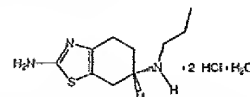
MIRAPEX®

[mir-ä-pex]
pramipexole
dihydrochloride tablets

DESCRIPTION

MIRAPEX Tablets contain pramipexole, a dopamine agonist indicated for the treatment of the signs and symptoms of idiopathic Parkinson's disease. The chemical name of pramipexole dihydrochloride is (S)-2-amino-4,5,6,7-tetrahydro-6-(propylamino)benzothiazole dihydrochloride monohydrate. Its empirical formula is $C_{10}H_{11}N_3S \cdot 2 HCl \cdot H_2O$, and its molecular weight is 302.27.

The structural formula is:



Pramipexole dihydrochloride is a white to off-white powder substance. Melting occurs in the range of 290° C to 301° C, with decomposition. Pramipexole dihydrochloride is more than 20% soluble in water, about 8% in methanol, about 0.5% in ethanol, and practically insoluble in dichloromethane.

MIRAPEX Tablets, for oral administration, contain 0.125 mg, 0.25 mg, 0.5 mg, 1.0 mg, or 1.5 mg of pramipexole dihydrochloride monohydrate. Inactive ingredients consist of mannitol, corn starch, colloidal silicon dioxide, povidone, and magnesium stearate.

CLINICAL PHARMACOLOGY

Pramipexole is a nonergot dopamine agonist with high relative in vitro specificity and full intrinsic activity at the D_2 subfamily of dopamine receptors, binding with higher affinity to D_2 than to D_1 or D_4 receptor subtypes. The relevance of D_2 receptor binding in Parkinson's disease is unknown. The precise mechanism of action of pramipexole as a treatment for Parkinson's disease is unknown, although it is believed to be related to its ability to stimulate dopamine receptors in the striatum. This conclusion is supported by electrophysiologic studies in animals that have demonstrated that pramipexole influences striatal neuronal firing rates via activation of dopamine receptors in the striatum and the substantia nigra, the site of neurons that send projections to the striatum.

Pharmacokinetics

Pramipexole is rapidly absorbed, reaching peak concentrations in approximately 2 hours. The absolute bioavailability of pramipexole is greater than 90%, indicating that it is well absorbed and undergoes little presystemic metabolism. Food does not affect the extent of pramipexole absorption, although the time of maximum plasma concentration (T_{max}) is increased by about 1 hour when the drug is taken with a meal.

Continued on next page

Information on these Pharmacia & Upjohn products is based on labeling in effect June 1, 1998. Further information concerning these and other Pharmacia & Upjohn products may be obtained by direct inquiry to Medical Information, Pharmacia & Upjohn, Kalamazoo, MI 49001.

Mirapex—Cont.

Pramipexole is extensively distributed, having a volume of distribution of about 500 L (coefficient of variation [CV]=20%). It is about 15% bound to plasma proteins. Pramipexole distributes into red blood cells as indicated by an erythrocyte-to-plasma ratio of approximately 2.

Pramipexole displays linear pharmacokinetics over the clinical dosage range. Its terminal half-life is about 8 hours in young healthy volunteers and about 12 hours in elderly volunteers (see CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations). Steady-state concentrations are achieved within 2 days of dosing.

Metabolism and elimination: Urinary excretion is the major route of pramipexole elimination, with 90% of a pramipexole dose recovered in urine, almost all as unchanged drug. Nonrenal routes may contribute to a small extent to pramipexole elimination, although no metabolites have been identified in plasma or urine. The renal clearance of pramipexole is approximately 400 mL/min (CV=25%), approximately three times higher than the glomerular filtration rate. Thus, pramipexole is secreted by the renal tubules, probably by the organic cation transport system.

Pharmacokinetics in Special Populations

Because therapy with pramipexole is initiated at a subtherapeutic dosage and gradually titrated upward according to clinical tolerability to obtain the optimum therapeutic effect, adjustment of the initial dose based on gender, weight, or age is not necessary. However, renal insufficiency, which can cause a large decrease in the ability to eliminate pramipexole, may necessitate dosage adjustment (see CLINICAL PHARMACOLOGY, Renal Insufficiency).

Gender: Pramipexole clearance is about 30% lower in women than in men, but most of this difference can be accounted for by differences in body weight. There is no difference in half-life between males and females.

Age: Pramipexole clearance decreases with age as the half-life and clearance are about 40% longer and 30% lower, respectively, in elderly (aged 65 years or older) compared with young healthy volunteers (aged less than 40 years). This difference is most likely due to the well-known reduction in renal function with age, since pramipexole clearance is correlated with renal function, as measured by creatinine clearance (see CLINICAL PHARMACOLOGY, Renal Insufficiency).

Parkinson's disease patients: A cross-study comparison of data suggests that the clearance of pramipexole may be reduced by about 30% in Parkinson's disease patients compared with healthy elderly volunteers. The reason for this difference appears to be reduced renal function in Parkinson's disease patients, which may be related to their poorer general health. The pharmacokinetics of pramipexole were comparable between early and advanced Parkinson's disease patients.

Pediatric: The pharmacokinetics of pramipexole in the pediatric population have not been evaluated.

Hepatic insufficiency: The influence of hepatic insufficiency on pramipexole pharmacokinetics has not been evaluated. Because approximately 90% of the recovered dose is excreted in the urine as unchanged drug, hepatic impairment would not be expected to have a significant effect on pramipexole elimination.

Renal insufficiency: The clearance of pramipexole was about 75% lower in patients with severe renal impairment (creatinine clearance approximately 20 mL/min) and about 60% lower in patients with moderate impairment (creatinine clearance approximately 40 mL/min) compared with healthy volunteers. A lower starting and maintenance dose is recommended in these patients (see PRECAUTIONS and DOSAGE AND ADMINISTRATION). In patients with varying degrees of renal impairment, pramipexole clearance correlates well with creatinine clearance. Therefore, creatinine clearance can be used as a predictor of the extent of decrease in pramipexole clearance. Pramipexole clearance is extremely low in dialysis patients, as a negligible amount of pramipexole is removed by dialysis. Caution should be exercised when administering pramipexole to patients with renal disease.

CLINICAL STUDIES

The effectiveness of MIRAPEX Tablets in the treatment of Parkinson's disease was evaluated in a multinational drug development program consisting of seven randomized, controlled trials. Three were conducted in patients with early Parkinson's disease who were not receiving concomitant levodopa, and four were conducted in patients with advanced Parkinson's disease who were receiving concomitant levodopa. Among these seven studies, three studies provide the most persuasive evidence of pramipexole's effectiveness in the management of patients with Parkinson's disease who were and were not receiving concomitant levodopa. Two of these three trials enrolled patients with early Parkinson's disease (not receiving levodopa), and one enrolled patients with advanced Parkinson's disease who were receiving maximally tolerated doses of levodopa.

In all studies, the Unified Parkinson's Disease Rating Scale (UPDRS), or one or more of its subparts, served as the primary outcome assessment measure. The UPDRS is a four-part multi-item rating scale intended to evaluate mentation (part I), activities of daily living (part II), motor performance (part III), and complications of therapy (part IV). Part II of the UPDRS contains 13 questions relating to activities of daily living (ADL), which are scored from 0 (normal) to 4 (maximal severity) for a maximum (worst) score of 52. Part III of the UPDRS contains 27 questions (for 14 items) and is scored as described for part II. It is designed to assess the severity of the cardinal motor findings in patients with Parkinson's disease (eg, tremor, rigidity, bradykinesia, postural instability, etc), scored for different body regions, and has a maximum (worst) score of 188.

Studies in Patients With Early Parkinson's Disease

Patients (N=599) in the two studies of early Parkinson's disease had a mean disease duration of 2 years, limited or no prior exposure to levodopa (generally none in the preceding 6 months), and were not experiencing the "on-off" phenomenon and dyskinesia characteristic of later stages of the disease.

One of the two early Parkinson's disease studies (N=335) was a double-blind, placebo-controlled, parallel trial consisting of a 7-week dose-escalation period and a 6-month maintenance period. Patients could be on selegiline, anticholinergics, or both, but could not be on levodopa products or amantadine. Patients were randomized to MIRAPEX or placebo. Patients treated with MIRAPEX had a starting daily dose of 0.375 mg and were titrated to a maximally tolerated dose, but no higher than 4.5 mg/day in three divided doses. At the end of the 6-month maintenance period, the mean improvement from baseline on the UPDRS part II (ADL) total score was 1.9 in the group receiving MIRAPEX and -0.4 in the placebo group, a difference that was statistically significant. The mean improvement from baseline on the UPDRS part III total score was 5.0 in the group receiving MIRAPEX and -0.8 in the placebo group, a difference that was also statistically significant. A statistically significant difference between groups in favor of MIRAPEX was seen beginning at week 2 of the UPDRS part II (maximum dose 0.75 mg/day) and at week 3 of the UPDRS part III (maximum dose 1.5 mg/day).

The second early Parkinson's disease study (N=264) was a double-blind, placebo-controlled, parallel trial consisting of a 6-week dose-escalation period and a 4-week maintenance period. Patients could be on selegiline, anticholinergics, amantadine, or any combination of these, but could not be on levodopa products. Patients were randomized to 1 of 4 fixed doses of MIRAPEX (1.5 mg, 3.0 mg, 4.5 mg, or 6.0 mg per day) or placebo. At the end of the 4-week maintenance period, the mean improvement from baseline on the UPDRS part II total score was 1.8 in the patients treated with MIRAPEX, regardless of assigned dose group, and 0.3 in placebo-treated patients. The mean improvement from baseline on the UPDRS part III total score was 4.2 in patients treated with MIRAPEX and 0.6 in placebo-treated patients. No dose-response relationship was demonstrated. The between-treatment differences on both parts of the UPDRS were statistically significant in favor of MIRAPEX for all doses.

No differences in effectiveness based on age or gender were detected. There were too few non-Caucasian patients to evaluate the effect of race. Patients receiving selegiline or anticholinergics had responses similar to patients not receiving these drugs.

Studies in Patients With Advanced Parkinson's Disease

In the advanced Parkinson's disease study, the primary assessments were the UPDRS and daily diaries that quantified amounts of "on" and "off" time.

Patients in the advanced Parkinson's disease study (N=360) had a mean disease duration of 9 years, had been exposed to levodopa for long periods of time (mean 8 years), used concomitant levodopa during the trial, and had "on-off" periods. The advanced Parkinson's disease study was a double-blind, placebo-controlled, parallel trial consisting of a 7-week dose-escalation period and a 6-month maintenance period. Patients were all treated with concomitant levodopa products and could additionally be on concomitant selegiline, anticholinergics, amantadine, or any combination. Patients treated with MIRAPEX had a starting dose of 0.375 mg/day and were titrated to a maximally tolerated dose, but no higher than 4.5 mg/day in three divided doses. At selected times during the 6-month maintenance period, patients were asked to record the amount of "off," "on," or "on with dyskinesia" time per day for several sequential days. At the end of the 6-month maintenance period, the mean improvement from baseline on the UPDRS part II total score was 2.7 in the group treated with MIRAPEX and 0.5 in the placebo group, a difference that was statistically significant. The mean improvement from baseline on the UPDRS part III total score was 5.6 in the group treated with MIRAPEX and 2.8 in the placebo group, a difference that was statistically significant. A statistically significant difference between groups in favor of MIRAPEX was seen at week 3 of the UPDRS part II (maximum dose 1.5 mg/day) and at week

2 of the UPDRS part III (maximum dose 0.75 mg/day). Dosage reduction of levodopa was allowed during this study if dyskinesia (or hallucinations) developed; levodopa dosage reduction occurred in 76% of patients treated with MIRAPEX versus 64% of placebo patients. On average, the levodopa dose was reduced 27%.

The mean number of "off" hours per day during baseline was 6 hours for both treatment groups. Throughout the trial, patients treated with MIRAPEX had a mean of 4 "off" hours per day, while placebo-treated patients continued to experience 6 "off" hours per day.

No differences in effectiveness based on age or gender were detected. There were too few non-Caucasian patients to evaluate the effect of race.

INDICATIONS AND USAGE

MIRAPEX Tablets are indicated for the treatment of the signs and symptoms of idiopathic Parkinson's disease.

The effectiveness of MIRAPEX was demonstrated in randomized, controlled trials in patients with early Parkinson's disease who were not receiving concomitant levodopa therapy as well as in patients with advanced disease on concomitant levodopa (see CLINICAL STUDIES).

CONTRAINDICATIONS

MIRAPEX Tablets are contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients.

WARNINGS

Symptomatic Hypotension: Dopamine agonists, in clinical studies and clinical experience, appear to impair the systemic regulation of blood pressure, with resulting orthostatic hypotension, especially during dose escalation. Parkinson's disease patients, in addition, appear to have an impaired capacity to respond to an orthostatic challenge. For these reasons, Parkinson's disease patients being treated with dopaminergic agonists ordinarily require careful monitoring for signs and symptoms of orthostatic hypotension, especially during dose escalation, and should be informed of this risk (see PRECAUTIONS, Information for Patients).

In clinical trials of pramipexole, however, and despite clear orthostatic effects in normal volunteers, the reported incidence of clinically significant orthostatic hypotension was not greater among those assigned to MIRAPEX Tablets than among those assigned to placebo. This result is clearly unexpected in light of the previous experience with the risks of dopamine agonist therapy.

While this finding could reflect a unique property of pramipexole, it might also be explained by the conditions of the study and the nature of the population enrolled in the clinical trials. Patients were very carefully titrated, and patients with active cardiovascular disease or significant orthostatic hypotension at baseline were excluded.

Hallucinations: In the three double-blind, placebo-controlled trials in early Parkinson's disease, hallucinations were observed in 9% (35 of 388) of patients receiving MIRAPEX, compared with 2.6% (6 of 235) of patients receiving placebo. In the four double-blind, placebo-controlled trials in advanced Parkinson's disease, where patients received MIRAPEX and concomitant levodopa, hallucinations were observed in 16.5% (43 of 260) of patients receiving MIRAPEX compared with 3.8% (10 of 264) of patients receiving placebo. Hallucinations were of sufficient severity to cause discontinuation of treatment in 3.1% of the early Parkinson's disease patients and 2.7% of the advanced Parkinson's disease patients compared with about 0.4% of placebo patients in both populations.

Age appears to increase the risk of hallucinations attributable to pramipexole. In the early Parkinson's disease patients, the risk of hallucinations was 1.9 times greater than placebo in patients younger than 65 years and 6.8 times greater than placebo in patients older than 65 years. In the advanced Parkinson's disease patients, the risk of hallucinations was 3.5 times greater than placebo in patients younger than 65 years and 5.2 times greater than placebo in patients older than 65 years.

PRECAUTIONS

Rhabdomyolysis: A single case of rhabdomyolysis occurred in a 49-year-old male with advanced Parkinson's disease treated with MIRAPEX Tablets. The patient was hospitalized with an elevated CPK (10,631 IU/L). The symptoms resolved with discontinuation of the medication.

Renal: Since pramipexole is eliminated through the kidneys, caution should be exercised when prescribing MIRAPEX to patients with renal insufficiency (see DOSAGE AND ADMINISTRATION).

Dyskinesia: MIRAPEX may potentiate the dopaminergic side effects of levodopa and may cause or exacerbate preexisting dyskinesia. Decreasing the dose of levodopa may ameliorate this side effect.

Retinal pathology in albino rats: Pathologic changes (degeneration and loss of photoreceptor cells) were observed in the retina of albino rats in the 2-year carcinogenicity study. Evaluation of the retinas of albino mice, pigmented rats, monkeys, and minipigs did not reveal similar changes. The potential significance of this effect in humans has not been

established, but cannot be disregarded because disruption of a mechanism that is universally present in vertebrates (ie, disk shedding) may be involved (see ANIMAL TOXICOLOGY).

Events Reported With Dopaminergic Therapy

Although the events enumerated below have not been reported in association with the use of pramipexole in its development program, they are associated with the use of other dopaminergic drugs. The expected incidence of these events, however, is so low that even if pramipexole caused these events at rates similar to those attributable to other dopaminergic therapies, it would be unlikely that even a single case would have occurred in a cohort of the size exposed to pramipexole in studies to date.

Withdrawal-emergent hyperpyrexia and confusion: Although not reported with pramipexole in the clinical development program, a symptom complex resembling the neuroleptic malignant syndrome (characterized by elevated temperature, muscular rigidity, altered consciousness, and autonomic instability), with no other obvious etiology, has been reported in association with rapid dose reduction, withdrawal of, or changes in antiparkinsonian therapy.

Fibrotic complications: Although not reported with pramipexole in the clinical development program, cases of retroperitoneal fibrosis, pulmonary infiltrates, pleural effusion, and pleural thickening have been reported in some patients treated with ergot-derived dopaminergic agents. While these complications may resolve when the drug is discontinued, complete resolution does not always occur.

Although these adverse events are believed to be related to the ergoline structure of these compounds, whether other, nonergot-derived dopamine agonists can cause them is unknown.

Information for Patients: Patients should be instructed to take MIRAPEX only as prescribed.

Patients should be informed that hallucinations can occur and that the elderly are at a higher risk than younger patients with Parkinson's disease.

Patients may develop postural (orthostatic) hypotension, with or without symptoms such as dizziness, nausea, fainting or blackouts, and sometimes, sweating. Hypotension may occur more frequently during initial therapy. Accordingly, patients should be cautioned against rising rapidly after sitting or lying down, especially if they have been doing so for prolonged periods and especially at the initiation of treatment with MIRAPEX.

Patients should be advised that MIRAPEX may cause somnolence and that they should neither drive a car nor operate other complex machinery until they have gained sufficient experience on MIRAPEX to gauge whether or not it affects their mental and/or motor performance adversely. Because of the possible additive sedative effects, caution should also be used when patients are taking other CNS depressants in combination with MIRAPEX.

Because the teratogenic potential of pramipexole has not been completely established in laboratory animals, and because experience in humans is limited, patients should be advised to notify their physicians if they become pregnant or intend to become pregnant during therapy (see PRECAUTIONS, Pregnancy).

Because of the possibility that pramipexole may be excreted in breast milk, patients should be advised to notify their physicians if they intend to breast-feed or are breast-feeding an infant.

If patients develop nausea, they should be advised that taking MIRAPEX with food may reduce the occurrence of nausea.

Laboratory Tests: During the development of MIRAPEX, no systematic abnormalities on routine laboratory testing were noted. Therefore, no specific guidance is offered regarding routine monitoring; the practitioner retains responsibility for determining how best to monitor the patient in his or her care.

Drug Interactions

Carbidopa/levodopa: Carbidopa/levodopa did not influence the pharmacokinetics of pramipexole in healthy volunteers (N=10). Pramipexole did not alter the extent of absorption (AUC) or the elimination of carbidopa/levodopa, although it caused an increase in levodopa C_{max} by about 40% and a decrease in T_{max} from 2.5 to 0.5 hours.

Selegiline: In healthy volunteers (N=11), selegiline did not influence the pharmacokinetics of pramipexole.

Amantadine: Population pharmacokinetic analysis suggests that amantadine is unlikely to alter the oral clearance of pramipexole (N=54).

Cimetidine: Cimetidine, a known inhibitor of renal tubular secretion of organic bases via the cationic transport system, caused a 50% increase in pramipexole AUC and a 40% increase in half-life (N=12).

Probenecid: Probenecid, a known inhibitor of renal tubular secretion of organic acids via the anionic transporter, did not noticeably influence pramipexole pharmacokinetics (N=12).

Other drugs eliminated via renal secretion: Population pharmacokinetic analysis suggests that coadministration of drugs that are secreted by the cationic transport system (eg,

cimetidine, ranitidine, diltiazem, triamterene, verapamil, quinidine, and quinine) decreases the oral clearance of pramipexole by about 20%, while those secreted by the anionic transport system (eg, cephalosporins, penicillins, indomethacin, hydrochlorothiazide, and chlorpropamide) are likely to have little effect on the oral clearance of pramipexole.

CYP interactions: Inhibitors of cytochrome P450 enzymes would not be expected to affect pramipexole elimination because pramipexole is not appreciably metabolized by these enzymes in vivo or in vitro. Pramipexole does not inhibit CYP enzymes CYP1A2, CYP2C9, CYP2C19, CYP2E1, and CYP3A4. Inhibition of CYP2D6 was observed with an apparent K_i of 30 μM, indicating that pramipexole will not inhibit CYP enzymes at plasma concentrations observed following the highest recommended clinical dose (1.5 mg tid).

Dopamine antagonists: Since pramipexole is a dopamine agonist, it is possible that dopamine antagonists, such as the neuroleptics (phenothiazines, butyrophenones, thioxanthenes) or metoclopramide, may diminish the effectiveness of MIRAPEX.

Drug/Laboratory Test Interactions: There are no known interactions between MIRAPEX and laboratory tests.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two-year carcinogenicity studies with pramipexole have been conducted in mice and rats. Pramipexole was administered in the diet to C57BL/6N mice at doses of 0.3, 2, and 10 mg/kg/day (0.3, 2.2, and 11 times the highest recommended clinical dose [1.5 mg tid] on a mg/m² basis). Pramipexole was administered in the diet to Wistar rats at 0.3, 2, and 8 mg/kg/day (plasma AUCs equal to 0.3, 2.5, and 12.5 times the AUC in humans receiving 1.5 mg tid). No significant increases in tumors occurred in either species.

Pramipexole was not mutagenic or clastogenic in a battery of assays, including the in vitro Ames assay, V79 gene mutation assay for HGPRT mutants, chromosomal aberration assay in Chinese hamster ovary cells, and in vivo mouse micronucleus assay.

In rat fertility studies, pramipexole at a dose of 2.5 mg/kg/day (5.4 times the highest clinical dose on a mg/m² basis), prolonged estrus cycles and inhibited implantation. These effects were associated with reductions in serum levels of prolactin, a hormone necessary for implantation and maintenance of early pregnancy in rats.

Pregnancy: Pregnancy Category C. When pramipexole was given to female rats throughout pregnancy, implantation was inhibited at a dose of 2.5 mg/kg/day (5.4 times the highest clinical dose on a mg/m² basis). Administration of 1.5 mg/kg/day of pramipexole to pregnant rats during the period of organogenesis (gestation days 7 through 16) resulted in a high incidence of total resorption of embryos. The plasma AUC in rats dosed at this level was 4.3 times the AUC in humans receiving 1.5 mg tid. These findings are thought to be due to the prolactin-lowering effect of pramipexole, since prolactin is necessary for implantation and maintenance of early pregnancy in rats (but not rabbits or humans). Because of pregnancy disruption and early embryonic loss in these studies, the teratogenic potential of pramipexole could not be adequately evaluated. There was no evidence of adverse effects on embryo-fetal development following administration of up to 10 mg/kg/day to pregnant rabbits during organogenesis (plasma AUC was 71 times that in humans receiving 1.5 mg tid). Postnatal growth was inhibited in the offspring of rats treated with 0.5 mg/kg/day (approximately equivalent to the highest clinical dose on a mg/m² basis) or greater during the latter part of pregnancy and throughout lactation.

There are no studies of pramipexole in human pregnancy. Because animal reproduction studies are not always predictive of human response, pramipexole should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

Nursing Mothers: A single-dose, radio-labeled study showed that drug-related materials were excreted into the breast milk of lactating rats. Concentrations of radioactivity in milk were three to six times higher than concentrations in plasma at equivalent time points.

Other studies have shown that pramipexole treatment resulted in an inhibition of prolactin secretion in humans and rats.

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from pramipexole, a decision should be made as to whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: The safety and efficacy of MIRAPEX in pediatric patients has not been established.

Geriatric Use: Pramipexole total oral clearance was approximately 30% lower in subjects older than 65 years compared with younger subjects, because of a decline in pramipexole renal clearance due to an age-related reduction in renal function. This resulted in an increase in elimination half-life from approximately 8.5 hours to 12 hours. In clinical studies, 38.7% of patients were older than 65 years.

There were no apparent differences in efficacy or safety between older and younger patients, except that the relative risk of hallucination associated with the use of MIRAPEX was increased in the elderly.

ADVERSE EVENTS

During the premarketing development of pramipexole, patients with either early or advanced Parkinson's disease were enrolled in clinical trials. Apart from the severity and duration of their disease, the two populations differed in their use of concomitant levodopa therapy. Patients with early disease did not receive concomitant levodopa therapy during treatment with pramipexole; those with advanced Parkinson's disease all received concomitant levodopa treatment. Because these two populations may have differential risks for various adverse events, this section will, in general, present adverse-event data for these two populations separately.

Because the controlled trials performed during premarketing development all used a titration design, with a resultant confounding of time and dose, it was impossible to adequately evaluate the effects of dose on the incidence of adverse events.

Early Parkinson's Disease

In the three double-blind, placebo-controlled trials of patients with early Parkinson's disease, the most commonly observed adverse events (>5%) that were numerically more frequent in the group treated with MIRAPEX Tablets were nausea, dizziness, somnolence, insomnia, constipation, asthenia, and hallucinations.

Approximately 12% of 388 patients with early Parkinson's disease and treated with MIRAPEX who participated in the double-blind, placebo-controlled trials discontinued treatment due to adverse events compared with 11% of 235 patients who received placebo. The adverse events most commonly causing discontinuation of treatment were related to the nervous system (hallucinations [3.1% on MIRAPEX vs 0.4% on placebo]; dizziness [2.1% on MIRAPEX vs 1% on placebo]; somnolence [1.6% on MIRAPEX vs 0% on placebo]; extrapyramidal syndrome [1.6% on MIRAPEX vs 6.4% on placebo]; headache and confusion [1.3% and 1.0%, respectively, on MIRAPEX vs 0% on placebo]; and gastrointestinal system [nausea [2.1% on MIRAPEX vs 0.4% on placebo]).

Adverse-event incidence in controlled clinical studies in early Parkinson's disease: Table 1 lists treatment-emergent adverse events that occurred in the double-blind, placebo-controlled studies in early Parkinson's disease that were reported by ≥1% of patients treated with MIRAPEX and were numerically more frequent than in the placebo group. In these studies, patients did not receive concomitant levodopa. Adverse events were usually mild or moderate in intensity.

The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical studies. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. However, the cited figures do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the adverse-event incidence rate in the population studied.

Table 1
Treatment-Emergent Adverse-Event* Incidence in
Double-Blind, Placebo-Controlled Trials in Early
Parkinson's Disease (Events ≥1% of Patients Treated With
MIRAPEX and Numerically More Frequent Than in the
Placebo Group)

Body System/ Adverse Event	MIRAPEX N=388	Placebo N=235
Body as a Whole		
Asthenia	14	12
General edema	5	3
Malaise	2	1
Reaction unvaluable	2	1
Fever	1	0
Digestive System		
Nausea	28	18
Constipation	14	6
Anorexia	4	2
Dysphagia	2	0

Continued on next page

Information on these Pharmacia & Upjohn products is based on labeling in effect June 1, 1998. Further information concerning these and other Pharmacia & Upjohn products may be obtained by direct inquiry to Medical Information, Pharmacia & Upjohn, Kalamazoo, MI 49001.

Mirapex—Cont.

Metabolic & Nutritional System		
Peripheral edema	5	4
Decreased weight	2	0
Nervous System		
Dizziness	25	24
Somnolence	22	9
Insomnia	17	12
Hallucinations	9	3
Confusion	4	1
Amnesia	4	2
Hypesthesia	3	1
Dystonia	2	1
Akathisia	2	0
Thinking abnormalities	2	0
Decreased libido	1	0
Myoclonus	1	0
Special Senses		
Vision abnormalities	3	0
Urogenital System		
Impotence	2	1

*Patients may have reported multiple adverse experiences during the study or at discontinuation; thus, patients may be included in more than one category.

Other events reported by 1% or more of patients with early Parkinson's disease and treated with MIRAPEX but reported equally or more frequently in the placebo group were infection, accidental injury, headache, pain, tremor, back pain, syncope, postural hypotension, hypertension, depression, abdominal pain, anxiety, dyspepsia, flatulence, diarrhea, rash, ataxia, dry mouth, extrapyramidal syndrome, leg cramps, twitching, pharyngitis, sinusitis, sweating, rhinitis, urinary tract infection, vasodilation, flu syndrome, increased saliva, tooth disease, dyspnea, increased cough, gait abnormalities, urinary frequency, vomiting, allergic reaction, hypertension, pruritus, hypokinesia, increased creatine PK, nervousness, dream abnormalities, chest pain, neck pain, paresthesia, tachycardia, vertigo, voice alteration, conjunctivitis, paralysis, accommodation abnormalities, tinnitus, diplopia, and taste perversions.

Advanced Parkinson's Disease

In the four double-blind, placebo-controlled trials of patients with advanced Parkinson's disease, the most commonly observed adverse events (>5%) that were numerically more frequent in the group treated with MIRAPEX and concomitant levodopa were postural (orthostatic) hypotension, dyskinesia, extrapyramidal syndrome, insomnia, dizziness, hallucinations, accidental injury, dream abnormalities, confusion, constipation, asthenia, somnolence, dystonia, gait abnormality, hypertension, dry mouth, amnesia, and urinary frequency.

Approximately 12% of 260 patients with advanced Parkinson's disease who received MIRAPEX and concomitant levodopa in the double-blind, placebo-controlled trials discontinued treatment due to adverse events compared with 16% of 264 patients who received placebo and concomitant levodopa. The events most commonly causing discontinuation of treatment were related to the nervous system (hallucinations [2.7% on MIRAPEX vs 0.4% on placebo]; dyskinesia [1.9% on MIRAPEX vs 0.8% on placebo]; extrapyramidal syndrome [1.5% on MIRAPEX vs 4.9% on placebo]; dizziness [1.2% on MIRAPEX vs 1.5% on placebo]; confusion [1.2% on MIRAPEX vs 2.3% on placebo]; and cardiovascular system (postural orthostatic hypotension [2.3% on MIRAPEX vs 1.1% on placebo]).

Adverse-event incidence in controlled clinical studies in advanced Parkinson's disease: Table 2 lists treatment-emergent adverse events that occurred in the double-blind, placebo-controlled studies in advanced Parkinson's disease that were reported by ≥1% of patients treated with MIRAPEX and were numerically more frequent than in the placebo group. In these studies, MIRAPEX or placebo was administered to patients who were also receiving concomitant levodopa. Adverse events were usually mild or moderate in intensity.

The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical studies. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. However, the cited figures do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse-events incidence rate in the population studied.

Table 2
Treatment-Emergent Adverse-Event* Incidence In Double-Blind, Placebo-Controlled Trials In Advanced Parkinson's Disease (Events ≥ 1% of Patients Treated With MIRAPEX and Numerically More Frequent Than in the Placebo Group)

Body System/ Adverse Event	MIRAPEX† N=260	Placebo† N=264
Body as a Whole		
Accidental injury	17	15
Asthenia	10	8
General edema	4	3
Chest pain	3	2
Malaise	3	2
Cardiovascular System		
Postural hypotension	53	48
Digestive System		
Constipation	10	9
Dry mouth	7	3
Metabolic & Nutritional System		
Peripheral edema	2	1
Increased creatine PK	1	0
Musculoskeletal System		
Arthritis	3	1
Twitching	2	0
Bursitis	2	0
Myasthenia	1	0
Nervous System		
Dyskinesia	47	31
Extrapyramidal syndrome	28	26
Insomnia	27	22
Dizziness	26	25
Hallucinations	17	4
Dream abnormalities	11	10
Confusion	10	7
Somnolence	9	6
Dystonia	8	7
Gait abnormalities	7	5
Hypertonia	7	6
Amnesia	6	4
Akathisia	3	2
Thinking abnormalities	3	2
Paranoid reaction	2	0
Delusions	1	0
Sleep disorders	1	0
Respiratory System		
Dyspnea	4	3
Rhinitis	3	1
Pneumonia	2	0
Skin & Appendages		
Skin disorders	2	1
Special Senses		
Accommodation abnormalities	4	2
Vision abnormalities	3	1
Diplopia	1	0
Urogenital System		
Urinary frequency	6	3
Urinary tract infection	4	3
Urinary incontinence	2	1

*Patients may have reported multiple adverse experiences during the study or at discontinuation; thus, patients may be included in more than one category.

†Patients received concomitant levodopa.

Other events reported by 1% or more of patients with advanced Parkinson's disease and treated with MIRAPEX but reported equally or more frequently in the placebo group were nausea, pain, infection, headache, depression, tremor, hypokinesia, anorexia, back pain, dyspepsia, flatulence, ataxia, flu syndrome, sinusitis, diarrhea, myalgia, abdominal pain, anxiety, rash, paresthesia, hypertension, increased saliva, tooth disorder, apathy, hypotension, sweating, vasodilation, vomiting, increased cough, nervousness, pruritus, hypesthesia, neck pain, syncope, arthralgia, dysphagia, palpitations, pharyngitis, vertigo, leg cramps, conjunctivitis, and lacrimation disorders.

Adverse Events: Relationship to Age, Gender, and Race: Among the treatment-emergent adverse events in patients treated with MIRAPEX, hallucination appeared to exhibit a positive relationship to age. No gender-related differences were observed. Only a small percentage (4%) of patients enrolled were non-Caucasian, therefore, an evaluation of adverse events related to race is not possible.

Other Adverse Events Observed During All Phase 2 and 3 Clinical Trials: MIRAPEX has been administered to 1,408 individuals during all clinical trials (Parkinson's disease and other patient populations), 648 of whom were in seven double-blind, placebo-controlled Parkinson's disease trials. During these trials, all adverse events were recorded by the clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse events, similar types of events were grouped into a smaller number of standardized categories using modified COSTART dictionary terminology. These categories are used in the listing below. The events listed below occurred in less than 1% of the 1,408 individuals exposed to MIRAPEX and occurred on at least two occasions (on one occasion if the event was serious). All reported events, except those already listed above, are included, without regard to determination of a causal relationship to MIRAPEX.

Events are listed within body-system categories in order of decreasing frequency.

Body as a whole: enlarged abdomen, death, fever, suicide attempt.

Cardiovascular system: peripheral vascular disease, myocardial infarction, angina pectoris, atrial fibrillation, heart failure, arrhythmia, atrial arrhythmia, pulmonary embolism.

Digestive system: thirst.

Musculoskeletal system: joint disorder, myasthenia.

Nervous system: agitation, CNS stimulation, hyperkinesia, psychosis, convulsions.

Respiratory system: pneumonia.

Special senses: cataract, eye disorder, glaucoma.

Urogenital system: dysuria, abnormal ejaculation, prostate cancer, hematuria, prostate disorder.

DRUG ABUSE AND DEPENDENCE

Pramipexole is not a controlled substance.

Pramipexole has not been systematically studied in animals or humans for its potential for abuse, tolerance, or physical dependence. However, in a rat model on cocaine self-administration, pramipexole had little or no effect.

OVERDOSAGE

There is no clinical experience with massive overdosage. One patient, with a 10-year history of schizophrenia, took 11 mg/day of pramipexole for 2 days; this is two to three times the protocol recommended daily dose. No adverse events were reported related to the increased dose. Blood pressure remained stable although pulse rate increased to between 100 and 120 beats/minute. The patient withdrew from the study at the end of week 2 due to lack of efficacy. There is no known antidote for overdosage of a dopamine agonist. If signs of central nervous system stimulation are present, a phenothiazine or other butyrophenone neuroleptic agent may be indicated; the efficacy of such drugs in reversing the effects of overdosage has not been assessed. Management of overdosage may require general supportive measures along with gastric lavage, intravenous fluids, and electrocardiogram monitoring.

DOSAGE AND ADMINISTRATION

In all clinical studies, dosage was initiated at a subtherapeutic level to avoid intolerable adverse effects and orthostatic hypotension. MIRAPEX should be titrated gradually in all patients. The dosage should be increased to achieve a maximum therapeutic effect, balanced against the principal side effects of dyskinesia, hallucinations, somnolence, and dry mouth.

Dosing in Patients With Normal Renal Function Initial Treatment: Dosages should be increased gradually from a starting dose of 0.375 mg/day given in three divided doses and should not be increased more frequently than every 5 to 7 days. A suggested ascending dosage schedule that was used in clinical studies is shown in the following table:

Ascending Dosage Schedule of MIRAPEX		
Week	Dosage (mg)	Total Daily Dose (mg)
1	0.125 tid	0.375
2	0.25 tid	0.75
3	0.5 tid	1.50
4	0.75 tid	2.25
5	1.0 tid	3.0
6	1.25 tid	3.75
7	1.5 tid	4.50

Maintenance Treatment: MIRAPEX Tablets were effective and well tolerated over a dosage range of 1.5 to 4.5 mg/day

administered in equally divided doses three times per day with or without concomitant levodopa (approximately 800 mg/day).

In a fixed-dose study in early Parkinson's disease patients, doses of 3 mg, 4.5 mg, and 6 mg per day of MIRAPEX were not shown to provide any significant benefit beyond that achieved at a daily dose of 1.5 mg/day.

When MIRAPEX is used in combination with levodopa, a reduction of the levodopa dosage should be considered. In a controlled study in advanced Parkinson's disease, the dosage of levodopa was reduced by an average of 27% from baseline.

Patients with Renal Impairment

Pramipexole Dosage in the Renally Impaired		
Renal Status	Starting Dose (mg)	Maximum Dose (mg)
Normal to mild impairment (creatinine CI > 60 mL/min)	0.125 tid	1.5 tid
Moderate impairment (creatinine CI = 35 to 59 mL/min)	0.125 bid	1.5 bid
Severe impairment (creatinine CI = 15 to 34 mL/min)	0.125 qd	1.5 qd
Very severe impairment (creatinine CI < 15 mL/min and hemodialysis patients)	The use of MIRAPEX has not been adequately studied in this group of patients.	

Discontinuation of Treatment: It is recommended that MIRAPEX be discontinued over a period of 1 week; in some studies, however, abrupt discontinuation was uneventful.

HOW SUPPLIED

MIRAPEX Tablets are available as follows:

0.125 mg: white, round tablet with "U" on one side and "2" on the reverse side.

Bottles of 63 NDC 0009-0002-02

0.25 mg: white, oval, scored tablet with "U" twice on one side and "4" twice on the reverse side.

Bottles of 80 NDC 0009-0004-02

Unit dose packages of 100 NDC 0009-0004-06

0.5 mg: white, oval, scored tablet with "U" twice on one side and "8" twice on the reverse side.

Bottles of 90 NDC 0009-0008-02

1 mg: white, round, scored tablet with "U" twice on one side and "16" twice on the reverse side.

Bottles of 90 NDC 0009-0006-02

Unit dose packages of 100 NDC 0009-0006-06

1.5 mg: white, round, scored tablet with "U" twice on one side and "37" twice on the reverse side.

Bottles of 90 NDC 0009-0037-02

Unit dose packages of 100 NDC 0009-0037-06

Store at 25°C (77°F); excursions permitted to 15°–30°C (59°–86°F) [see USP Controlled Room Temperature]. Protect from light.

Rx only

ANIMAL TOXICOLOGY

Retinal Pathology in Albino Rats

Pathologic changes (degeneration and loss of photoreceptor cells) were observed in the retina of albino rats in the 2-year carcinogenicity study with pramipexole. These findings were first observed during week 76 and were dose dependent in animals receiving 2 or 8 mg/kg/day (plasma AUCs equal to 2.5 and 12.5 times the AUC in humans that received 1.5 mg tid). Similar findings were not present in rats receiving 0.3 mg/kg/day (plasma AUC equal to 0.3 times the AUC in humans that received 1.5 mg tid).

Investigative studies demonstrated that pramipexole reduced the rate of disk shedding from the photoreceptor rod cells of the retina in albino rats, which was associated with enhanced sensitivity to the damaging effects of light. In a comparative study, degeneration and loss of photoreceptor cells occurred in albino rats after 13 weeks of treatment with 25 mg/kg/day of pramipexole (64 times the highest clinical dose on a mg/m² basis) and constant light (100 lux) but not in pigmented rats exposed to the same dose and higher light intensities (500 lux). Thus, the retina of albino rats is considered to be uniquely sensitive to the damaging effects of pramipexole and light. Similar changes in the retina did not occur in a 2-year carcinogenicity study in albino mice treated with 0.3, 2, or 10 mg/kg/day (0.3, 2.2 and 11 times the highest clinical dose on a mg/m² basis). Evalua-

tion of the retinas of monkeys given 0.1, 0.5, or 2.0 mg/kg/day of pramipexole (0.4, 2.2, and 8.6 times the highest clinical dose on a mg/m² basis) for 12 months and minipigs given 0.3, 1, or 5 mg/kg/day of pramipexole for 13 weeks also detected no changes.

The potential significance of this effect in humans has not been established, but cannot be disregarded because disruption of a mechanism that is universally present in vertebrates (ie, disk shedding) may be involved.

Fibro-osseous Proliferative Lesions in Mice

An increased incidence of fibro-osseous proliferative lesions occurred in the femurs of female mice treated for 2 years with 0.3, 2.0, or 10 mg/kg/day (0.3, 2.2, and 11 times the highest clinical dose on a mg/m² basis). Lesions occurred at a lower rate in control animals. Similar lesions were not observed in male mice or rats and monkeys of either sex that were treated chronically with pramipexole. The significance of this lesion to humans is not known.

Pharmacia & Upjohn Company

Kalamazoo, Michigan 49001, USA

Revised March 1998

817 017 004

691439

Shown in Product Identification Guide, page 332

MYCOBUTIN®

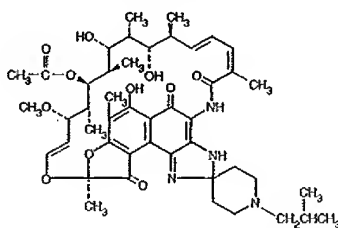
(Rifabutin Capsules, USP)

Rx

DESCRIPTION

MYCOBUTIN® is the brand name for the antimycobacterial agent rifabutin. It is a semisynthetic ansamycin antibiotic derived from rifamycin S. MYCOBUTIN capsules for oral administration contain 150 mg of Rifabutin, USP per capsule, along with the inactive ingredients microcrystalline cellulose, magnesium stearate, red iron oxide, silica gel, sodium lauryl sulfate, titanium dioxide, and edible white ink.

The chemical name for rifabutin is 1',4'-dihydro-1'-deoxy-1,4'-dihydro-5'-(2-methylpropyl)-1-oxorifamycin XIV (Chemical Abstracts Service, 9th Collective Index) or (9S, 12E, 14S, 15R, 16S, 17R, 18R, 19R, 20S, 21S, 22E, 24Z)-6, 16, 18, 20-tetrahydroxy-1'-isobutyl-14-methoxy-7,9,15,17,19,21,25-heptamethyl-spiro [9,4]-[epoxypentadecal-11, 13]-[trienimino]-2H-furo[2',3':7,8]naphth[1,2-d]imidazole-2,4'-piperidine)-5,10,26-(3H,9H)-trione-16-acetate. Rifabutin has a molecular formula of C₄₆H₅₂N₂O₁₁, a molecular weight of 847.02 and the following structure:



Rifabutin is a red-violet powder soluble in chloroform and methanol, sparingly soluble in ethanol, and very slightly soluble in water (0.19 mg/mL). Its log P value (the base 10 logarithm of the partition coefficient between n-octanol and water) is 3.2 (n-octanol/water).

CLINICAL PHARMACOLOGY

Pharmacokinetics

Following a single oral dose of 300 mg to nine healthy adult volunteers, MYCOBUTIN was readily absorbed from the gastrointestinal tract with mean (±SD) peak plasma levels (C_{max}) of 375 (±267) ng/mL (range: 141 to 1039 ng/mL) attained in 3.3 (±0.9) hours (T_{max} range: 2 to 4 hours). Plasma concentrations post-C_{max} declined in an apparent biphasic manner. Kinetic dose-proportionality has been established over the 300 to 600 mg dose range in nine healthy adult volunteers (crossover design) and in 16 early symptomatic human immunodeficiency virus (HIV)-positive patients over a 300 to 900 mg dose range. Rifabutin was slowly eliminated from plasma in seven healthy adult volunteers, presumably because of distribution-limited elimination, with a mean terminal half-life of 45 (±17) hours (range: 16 to 69 hours). Although the systemic levels of rifabutin following multiple dosing decreased by 38%, its terminal half-life remained unchanged. Rifabutin, due to its high lipophilicity, demonstrates a high propensity for distribution and intracellular tissue uptake. Estimates of apparent steady-state distribution volume (9.3 ± 1.5 L/kg) in five HIV-positive patients, following I.V. dosing, exceed total body water by approximately 15-fold. Substantially higher intracellular tissue levels than those seen in plasma have been observed in both rat and man. The lung to plasma concentration ratio, obtained at 12 hours, was found to be approximately 6.5 in

four surgical patients administered an oral dose. Mean rifabutin steady-state trough levels (C_{min}^{ss}; 24-hour post-dose) ranged from 50 to 65 ng/mL in HIV-positive patients and in healthy adult volunteers. About 85% of the drug is bound in a concentration-independent manner to plasma proteins over a concentration range of 0.05 to 1 µg/mL. Binding does not appear to be influenced by renal or hepatic dysfunction.

Mean systemic clearance (CL_s/F) in healthy adult volunteers following a single oral dose was 0.69 (±0.32) L/hr/kg (range: 0.46 to 1.34 L/hr/kg). Renal and biliary clearance of unchanged drug each contribute approximately 5% to CL_s/F. About 30% of the dose is excreted in the feces. A mass-balance study in three healthy adult volunteers with ¹⁴C-labeled drug has shown that 53% of the oral dose was excreted in the urine, primarily as metabolites. Of the five metabolites that have been identified, 25-O-desacetyl and 31-hydroxy are the most predominant, and show a plasma metabolite:parent area under the curve ratio of 0.10 and 0.07, respectively. The former has an activity equal to the parent drug and contributes up to 10% to the total antimicrobial activity.

Absolute bioavailability assessed in five HIV-positive patients, who received both oral and I.V. doses, averaged 20%. Total recovery of radioactivity in the urine indicates that at least 53% of the orally administered rifabutin dose is absorbed from the G.I. tract. The bioavailability of rifabutin from the capsule dosage form, relative to a solution, was 85% in 12 healthy adult volunteers. High-fat meals slow the rate without influencing the extent of absorption from the capsule dosage form. The overall pharmacokinetics of MYCOBUTIN are modified only slightly by alterations in hepatic function or age. MYCOBUTIN steady-state kinetics in early symptomatic HIV-positive patients are similar to healthy volunteers. Compared to healthy volunteers, steady-state kinetics of MYCOBUTIN are more variable in elderly patients (>70 years) and in symptomatic HIV-positive patients. Somewhat reduced drug distribution and faster elimination of rifabutin in patients with compromised renal function may result in decreased drug concentrations. The clinical implications of this are unknown.

No rifabutin disposition information is currently available in children or adolescents under 18 years of age.

Microbiology

Mechanism of Action

Rifabutin inhibits DNA-dependent RNA polymerase in susceptible strains of *Escherichia coli* and *Bacillus subtilis* but not in mammalian cells. In resistant strains of *E. coli*, rifabutin, like rifampin, did not inhibit this enzyme. It is not known whether rifabutin inhibits DNA-dependent RNA polymerase in *Mycobacterium avium* or in *M. intracellulare* which comprise *M. avium* complex (MAC).

Susceptibility Testing

In vitro susceptibility testing methods and diagnostic products used for determining minimum inhibitory concentration (MIC) values against *M. avium* complex (MAC) organisms have not been standardized. Breakpoints to determine whether clinical isolates of MAC and other mycobacterial species are susceptible or resistant to rifabutin have not been established.

In Vitro Studies

Rifabutin has demonstrated *in vitro* activity against *M. avium* complex (MAC) organisms isolated from both HIV-positive and HIV-negative people. While gene probe techniques may be used to identify these two organisms, many reported studies did not distinguish between these two species. The vast majority of isolates from MAC-infected, HIV-positive people are *M. avium*, whereas in HIV-negative people, about 40% of the MAC isolates are *M. intracellulare*. Various *in vitro* methodologies employing broth or solid media, with and without polysorbate 80 (Tween 80), have been used to determine rifabutin MIC values for mycobacterial species. In general, MIC values determined in broth are several fold lower than that observed with methods employing solid media. Utilization of Tween 80 in these assays has been shown to further lower MIC values. However, MIC values were substantially higher for egg based compared to agar based solid media.

Rifabutin activity against 211 MAC isolates from HIV-positive people was evaluated *in vitro* utilizing a radiometric broth and an agar dilution method. Results showed that 78% and 82% of these isolates had MIC₉₀ values of ≤0.25 µg/mL and ≤1.0 µg/mL, respectively, when evaluated by these two methods. Rifabutin was also shown to be active against phagocytized, *M. avium* complex in a mouse macrophage cell culture model.

Continued on next page

Information on these Pharmacia & Upjohn products is based on labeling in effect June 1, 1998. Further information concerning these and other Pharmacia & Upjohn products may be obtained by direct inquiry to Medical Information, Pharmacia & Upjohn, Kalamazoo, MI 49001.